

Infection with SARS-CoV-2 among children with asthma: evidence from Global Asthma Network

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Abstract

Background

Clinical presentations of coronavirus disease 2019 (COVID-19) among children with asthma have rarely been investigated. This study aimed to assess clinical manifestations and outcome of COVID-19 among children with asthma, and whether the use of asthma medications was associated with outcomes of interest.

Methods

The Global Asthma Network (GAN) conducted a global survey among GAN centers. Data collection was between November 2020 and April 2021.

Results

Fourteen GAN centers from 10 countries provided data on 169 children with asthma infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 was asymptomatic in 58 (34.3%), mild in 93 (55.0%), moderate in 14 (8.3%), and severe/critical in 4 (2.4%). Thirty-eight (22.5%) patients had exacerbation of asthma and 21 (12.4%) were hospitalized for a median of 7 days (interquartile range 3–16). Those who had moderate or more severe COVID-19 were significantly more likely to have exacerbation of asthma as compared to those who were asymptomatic or had mild COVID-19 (adjusted odds ratio (adjOR) 3.97, 95% CI 1.23–12.84). Those who used inhaled bronchodilators were significantly more likely to have a change of asthma medications (adjOR 2.39, 95% CI 1.02–5.63) compared to those who did not. Children who used inhaled corticosteroids (ICS) did not differ from those who did not use ICS with regard to being symptomatic, severity of COVID-19, asthma exacerbation, and hospitalization.

Conclusions

Over dependence on inhaled bronchodilator may be inappropriate. Use of ICS may be safe and should be continued in children with asthma during the pandemic of COVID-19.

Key message

Our study reports that the use of inhaled corticosteroid (ICS) was not associated with severity of COVID-19, exacerbations of asthma, a change of asthma medications, and hospitalization in children infected with SARS-CoV-2; this clearly supports the recommendation of continuation of the use of ICS among patients with asthma during the pandemic of COVID-19.

1 INTRODUCTION

Severe acute respiratory syndrome (SARS) caused by a novel coronavirus (SARS-CoV-1) mainly caused symptomatic infections in adults. Children appear to be less susceptible to SARS-CoV-1 and have a better prognosis on follow-up.^{1, 2} During the 2003 outbreak of SARS, there appeared to be a low rate of asthma exacerbations among children with asthma in Singapore, likely due to a reduced incidence of acute respiratory infection.³ The non-SARS coronaviruses were the second most important cause of the common cold after rhinoviruses, causing exacerbations of asthma among children aged 5 years or older.^{4, 5} It has been hypothesized that SARS-CoV-1 may be less likely to induce asthma attacks in children.³

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is predominant in adults.^{6, 7} Children and adolescents are less likely to have severe COVID-19 and have a lower case-fatality rate than adults.^{6, 8} Although clinical presentations and outcomes of COVID-19 in children have been reported, information on SARS-CoV-2 and childhood asthma is limited.^{7, 9, 10} Previous studies on the association between asthma and COVID-19 did not report consistent findings.¹¹⁻¹³ Some studies reported that asthma was not a risk factor for hospitalization in patients with COVID-19,¹⁴⁻¹⁶ others reported that asthma was associated with increased risk of intubation and mortality.^{17, 18} Studies reported that during the pandemic of COVID-19, children with asthma experienced fewer upper respiratory tract infections, emergency visits, asthma attacks, and hospitalizations due to asthma, probably due to public health interventions leading to reduced exposure to asthma triggers.¹⁹ Whether there is increased morbidity of COVID-19 among children with asthma remains unknown.¹³ Furthermore, it is unclear whether SARS-CoV-2, like non-SARS coronaviruses, is associated with exacerbations of asthma.

To improve understanding of COVID-19 and childhood asthma, the Global Asthma Network (GAN²⁰) Steering Group conducted a global survey among its worldwide network aiming to

assess clinical manifestations and outcome of COVID-19 among children with asthma, including severity of COVID-19, exacerbation of asthma and change of asthma medicine, and hospitalization. We hypothesized that the use of asthma medications may be associated with severity of COVID-19, exacerbation of asthma, change of asthma medications, and hospitalization among children with asthma infected with SARS-CoV-2.

2 METHODS

The study population was children with asthma infected with SARS-CoV-2 confirmed by reverse transcription polymerase chain reaction (RT-PCR) tests. Detection of antibodies to SARS-CoV-2 may not indicate acute infection. Therefore, serologic assays were not used to confirm acute infection with SARS-CoV-2. A structured questionnaire was developed to collect data on: (1) patient characteristics and comorbidity; (2) medicines used to control asthma in the past three months before a positive test of SARS-CoV-2; (3) clinical manifestations of infection with SARS-CoV-2; (4) exacerbation of asthma within 10 days of a positive test for SARS-CoV-2 and change of asthma medications associated with SARS-CoV-2 infection; and (5) treatment and outcome of COVID-19 (eMethods in Appendix [S2](#)).

Information about the survey of childhood asthma and COVID-19 was sent to 336 GAN collaborators in 137 countries in September 2020 to solicit an expression of interest (EOI) for inclusion. A total of 48 GAN centers from 33 countries replied positively to the EOI, and the questionnaire was sent to those collaborators on 2nd November 2020. Data collection was closed on 28th April 2021. The minimum interval between the date of positive SARS-CoV-2 test and the date of survey conducted was 10 days and the median (interquartile range) interval was 103 (45–188) days.

The sampling frame included asthmatic children who have been tested for SARS-CoV-2 in contact examinations, in a clinical practice, or in a hospital of the participating centers. All asthmatic children who tested positive for SARS-CoV-2 were included, regardless of symptoms.

The GAN Global Centre, Auckland, New Zealand, coordinated the study.²¹ The questionnaire was developed into a web-based data entry platform which was placed on the GAN website for direct data entry by GAN centers.

2.1 Definitions

The structured questionnaire provided definitions of tachypnea,⁶ tachycardia,⁶ and severity of COVID-19.⁹ Children were defined as those aged <18 years. Exacerbation of asthma was determined by the relevant clinician taking care of the patients. Change of asthma medications included prescription of a new medication (new prescription), increased dosage and increased frequency of inhaled short-acting beta-agonist (SABA), inhaled long-acting beta-agonist (LABA), ICS, corticosteroid, and bronchodilator in a combined inhaler (combined inhaler), and leukotriene receptor antagonist (LTRA).

2.2 Data analysis

Stata version 15 (Stata Corp LP, College Station, Texas) was used for statistical analyses. Clinical manifestations, management and outcomes of COVID-19, medications used for asthma management and change of asthma medications associated with SARS-CoV-2 infection were analyzed. Countries were categorized into high-income countries (Greece, Saudi Arabia, and Spain) and other countries according to the World Bank. Because the number of patients treated with LABA was relatively small, LABA and SABA were combined as “inhaled bronchodilators” in the analysis. Asthma medication administered as needed and daily was combined as “use of each asthma medication.” Change of asthma medications, including new prescription, increased dosage, and increased frequency, was combined as “change of asthma medications.” Categorical data were compared by using the Pearson χ^2 test. Logistic regression models were constructed to assess factors associated with being symptomatic, severity of COVID-19 (asymptomatic/mild vs moderate/severe), exacerbation of asthma, change of asthma medications, and hospitalization to obtain odds ratio (OR) and 95% confidence interval, and the probability levels in the logistic regression analysis were for two-sided tests. All analyses were adjusted for age, sex, and countries as these were considered a priori to be potential confounders. We initially conducted “univariable” analyses assessing each variable in turn (adjusted for age, sex, and countries). We then ran a “full” model, with each factor being adjusted for age, sex, countries, and all other variables that were considered. We then checked the standard errors for each variable estimate to check whether there were problems of collinearity.²² We found that there were problems of collinearity when different asthma medications (use of inhaled bronchodilators, use of ICS, use of combined inhaler, and use of LTRA) were entered into the model at the same time. We therefore ran separate models for each asthma medication, adjusted for age, sex, countries, exposure to COVID-19 cases, comorbidity, and severity of COVID-19.

2.3 Ethics

Before starting the study, all participating centers were required to attain approval from their ethics committee.

3 RESULTS

Fourteen GAN centers from 10 countries (Argentina, Belarus, Brazil, Greece, Guatemala, Iran, Kyrgyzstan, the Kingdom of Saudi Arabia, Spain, and Sudan) provided data on a total of 177 asthmatic children infected with SARS-CoV-2. Of the 177 cases, 169 were diagnosed by RT-PCR tests; the six by antibody test and two by antigen test were excluded. We retained for analysis 169 asthmatic children whose infection was confirmed by RT-PCR tests. Of the 169 children, 110 (65.1%) were male, 128 (75.7%) aged 5–13.9 years, 121 (71.6%) had known exposure to COVID-19 cases in the family, and 29 (17.2%) had comorbidities other than asthma (Table 1; eTable 1 in Appendix S2).

TABLE 1. Characteristics of 169 asthmatic children infected with SARS-CoV-2

	Number	Percentage
Total	169	100
Country		
Spain	93	55.0
Argentina	16	9.5
Kyrgyzstan	14	8.3
Iran	12	7.1
Saudi Arabia	9	5.3
Others ^a	25	14.8
Location of case identification		
A clinical practice of the participant	18	10.7
A hospital or other medical facility	130	76.9
Household contact examination	15	8.9
School-based contact examination	3	1.8
Others ^b	3	1.8
Specimen used for testing		

^a Greece, 7; Brazil, 6; Sudan, 5; Guatemala, 4; Belarus, 3.

^b extended family, 1; community contact examination, 1; telemedicine, 1.

^c RT-PCR, reverse transcription polymerase chain reaction; TaqPath COVID-19 CE-IVD, 5; Procleix SARS-CoV-2 Assay, 5; Biomol one-step COVID-19, 1.

^d School, 12; relatives, 5; pleasure activities, 5; friend, 1; soccer camp, 1; homeschool teacher, 1; martial arts academy, 1.

Of the 169 children, 111 (65.7%) were symptomatic and 76 (45.0%) had body temperature >37.5°C. Common symptoms included cough (43.8%), headache (42.0%), rhinorrhoea (34.9%), fatigue (34.3%), and smell reduction (25.4%) (eTable 1 in Appendix [S2](#)).

Thirty-eight (22.5%) patients had exacerbations of asthma within 10 days of a positive test for SARS-CoV-2; 53 (31.4%) had a change of asthma medications associated with SARS-CoV-2

infection, including new prescription or increased dosage or increased frequency of inhaled SABA in 41 (24.3%), inhaled LABA in 5 (3.0%), ICS in 22 (13.0%), combined inhaler in 15 (8.9%), and LTRA in 6 (3.6%) (Table 2).

TABLE 2. Change of asthma medications, severity, treatment and outcomes of COVID-19 in asthmatic children infected with SARS-CoV-2

	Number	Percentage
Total	169	100
Treatment change	53	31.4
Short acting β - agonists (SABA)	41	24.3
New prescription	12	7.1
Increased dosage	6	3.6
Increased frequency	24 ^a	14.2
Long acting β -agonists (LABA)	5	3.0
New prescription	2	1.2
Increased dosage	0	0
Increased frequency	3	1.8
Inhaled corticosteroid (ICS)	22	13.0
New prescription	12 ^b	7.1
Increased dosage	8	4.7
Increased frequency	2	1.2
Combination ICS and LABA	15	8.9

^a one patient had both increased dosage and increased frequency

^b one patient was prescribed budesonide nebulization

^c Pneumonia detected by chest radiograph in 9 cases, by chest computed tomography in 6, by both chest radiograph and chest computed tomography in 3.

^d CPAP, continuous positive airways pressure; BiPAP, bilevel positive airways pressure.

COVID-19 was asymptomatic in 58 (34.3%), mild in 93 (55.0%), moderate in 14 (8.3%), and severe/critical in 4 (2.4%). 21 (12.4%) patients had been hospitalized for a median of seven

days (interquartile range 3–16). One (0.6%) received remdesivir; 19 (11.2%) received systemic (oral and/or intravenous) steroids. One (0.6%) patient aged 16 died on the 6th day of hospitalization. Ten (5.9%) patients had sequelae, including persisted respiratory symptoms ($n = 4$), decline of lung function ($n = 5$), and hair loss and weight loss ($n = 1$).

Adolescents aged 14 years or older were significantly more likely to be symptomatic than children aged under 10 years (adjusted odds ratio (adjOR) 10.64, 95% confidence interval (CI) 2.14–52.95) (eTable 2 in Appendix [S2](#)). Patients from high-income countries were significantly less likely to be symptomatic than patients from other countries (adjOR 0.08, 95% CI 0.03–0.26). Use of ICS (adjOR 0.80, 95% CI 0.36–1.76) and other asthma medications were not significantly associated with being symptomatic.

Patients from high-income countries were significantly less likely to have moderate or more severe COVID-19 than patients from other countries (adjOR 0.03, 95% CI <0.01–0.23) (Table [3](#)). Use of ICS (adjOR 1.11, 95% CI 0.26–4.80) and other asthma medications were not significantly associated with moderate or more severe COVID-19.

TABLE 3. Factors associated with moderate/severe/critical COVID-19

	Total N=	Moderate/severe /critical N (%)	Univariable OR(95% CI)	Multivariable adjOR(95% CI)
Total	169	18 (10.7)		
Age at infection (years)				
<5	17	3 (17.7)	reference	reference
5–9.9	68	3 (4.4)	0.24 (0.04–1.59)	0.27 (0.04–1.91)
10–13.9	60	7 (11.7)	0.63 (0.12–3.41)	0.65 (0.11–3.66)
≥14	24	5 (20.8)	1.12 (0.18–7.06)	1.04 (0.15–7.10)
Sex				
Female	59	6 (10.2)	reference	reference
Male	110	12(10.9)	1.00 (0.31–3.26)	0.84 (0.24–2.92)
High-income countries				
No	60	17 (28.3)	reference	reference
Yes	109	1 (0.9)	0.03 (<0.01–0.19)	0.03 (<0.01–0.23)

Abbreviations: OR, odds ratio; adjusted for age and sex; adjOR, adjusted OR; adjusted for age, sex, exposure to COVID-19 cases, comorbidity, and severity of COVID-19.

^a Inhaled short-acting beta agonist or long acting beta agonist. ^b Daily or as needed.

Those who had moderate or more severe COVID-19 were significantly more likely to have exacerbation of asthma within 10 days of a positive test for SARS-CoV-2 as compared to those who were asymptomatic or had mild COVID-19 (adjOR 3.97, 95% CI 1.23–12.84) (Table 4). Use of ICS (adjOR 2.04, 95% CI 0.84–4.98) and other asthma medications were not significantly associated with asthma exacerbation.

TABLE 4. Factors associated with asthma exacerbation with SARS-CoV-2 infection

	Total N=	Exacerbation N (%)	Univariable OR(95% CI)	Multivariable adjOR(95% CI)
Total	169	38 (22.5)		
Age at infection (years)				
<5	17	5 (29.4)	reference	Reference
5–9.9	68	12 (17.7)	0.58 (0.17–2.08)	0.70 (0.18–2.74)
10–13.9	60	14 (23.3)	0.77 (0.22–2.69)	0.81 (0.21–3.08)
≥14	24	7 (29.2)	0.93 (0.22–3.88)	0.97 (0.2–4.47)
Sex				
Female	59	15 (25.4)	reference	reference
Male	110	23 (20.9)	0.76 (0.35–1.66)	0.74 (0.32–1.69)
High income countries				
No	60	23 (38.3)	reference	reference
Yes	109	15 (13.8)	0.27 (0.12–0.57)	0.45 (0.19–1.09)
Exposure to COVID-19 cases				
Unknown	22	7 (31.8)	reference	reference

Abbreviations: adjOR, adjusted OR; adjusted for age and sex; adjusted for age, sex, exposure to COVID-19 cases, comorbidity, and severity of COVID-19; OR, odds ratio.

^a Inhaled short-acting beta agonist or long acting beta agonist ^b daily or as needed

Patients from high-income countries were significantly less likely to have a change of asthma medications than patients from other countries (adjOR 0.27, 95% CI 0.12–0.60) (eTable 3 in Appendix [S2](#)). Those with known exposure outside family to COVID-19 cases were significantly less likely to have a change of asthma medications than those without documented exposure to COVID-19 cases (adjOR 0.16, 95% CI 0.03–0.87). Patients who used inhaled bronchodilators were significantly more likely to have a change of asthma medications as compared to those who did not (adjOR 2.39, 95% CI 1.02–5.63). Use of ICS (adjOR 1.92, 95% CI 0.82–4.52), use of a combined inhaler, and use of LTRA were not significantly associated with a change of asthma medications.

Patients from high-income countries were significantly less likely to be hospitalized as compared to patients from other countries (adjOR 0.03, 95% CI <0.01–0.31) (eTable 4 in Appendix [S2](#)). Those who had moderate or more severe COVID-19 were significantly more likely to be hospitalized as compared to those who were asymptomatic or mild COVID-19 (adjOR 24.62, 95% CI 4.63–130.90). Use of ICS (adjOR 2.88, 95% CI 0.47–17.73) and other asthma medications were not significantly associated with hospitalization.

4 DISCUSSION

We have assessed clinical manifestations and outcome of infection with SARS-CoV-2 in a large number of children with asthma. We found that about 90% of asthmatic children were asymptomatic or had mild COVID-19. However, a substantial proportion of children had exacerbations of asthma within 10 days of a positive test for SARS-CoV-2 and a considerable proportion had a change of asthma medications associated with infection with SARS-CoV-2.

The proportions of COVID-19 cases who were asymptomatic among children varies between previously published studies, ranging from 13% to 28%^{7, 9, 23, 24}; these proportions are generally higher than that observed in adults.²⁵ About 35% of our study population were asymptomatic, in part because a high proportion of children had known exposure to COVID-19 cases and those who were found to be infected during contact examinations, regardless of symptoms, were included. The proportions of symptomatic cases increased with age, and adolescents were less likely to be asymptomatic than younger children. Patients from high-income countries were significantly more likely to be asymptomatic, likely because of a better laboratory capacity of testing of SARS-CoV-2 in high-income countries.

Severity of COVID-19 among children varied between studies. The proportion of children with mild COVID-19 ranged from 20% to 58%; moderate disease ranged from 19% to 64.9%; and 2% to 3% had severe/critical illness.^{7, 23, 24} Garazzino et al reported that of the 168 laboratory-confirmed COVID-19 cases, 15.5% had pneumonia.²⁶ Tagarro et al. reported that among 41 pediatric COVID-19 cases, 10% required oxygen support beyond nasal

prongs.²⁷ Compared with previous reports on COVID-19 in children, our study revealed that asthmatic children did not appear to have a higher frequency of severe COVID-19, consistent with the finding of Zachariah et al that the proportion of patients with asthma was not significantly different between severe and non-severe cases.¹⁰ Studies reported that patients with chronic respiratory disease were significantly under-represented among hospitalized COVID-19 cases.¹¹ Our findings suggest that this was likely because the majority of patients with asthma had mild COVID-19. Of note is that use of ICS and other asthma medications were not significantly associated with severity COVID-19.

In our study, a substantial proportion of asthmatic children had exacerbations of asthma and a considerable proportion had a change of asthma medications. However, the severity of COVID-19 was significantly associated with exacerbation of asthma. Whether symptoms experienced by patients were caused by COVID-19 or due to exacerbation of asthma was less clear. Our study revealed that the use of inhaled bronchodilator was associated with a change of asthma medications, likely indicating that their asthma was not appropriately controlled. However, the use of ICS was not associated with asthma exacerbation or a change of asthma medications. Ramakrishnan et al hypothesized that the use of ICS may be protective against severe COVID-19 and reported that in a randomized controlled trial early administration of inhaled budesonide reduced the need of urgent medical care and reduced time to recovery after early COVID-19.²⁸ Izquierdo et al reported that the use of ICS was lower in adults with asthma who required hospitalization due to COVID-19, as compared to non-hospitalized patients.²⁹ Our study reports that the use of ICS was not associated with severity of COVID-19, exacerbations of asthma, a change of asthma medications and hospitalization in children infected with SARS-CoV-2; this clearly supports the recommendation of continuation of the use of ICS among patients with asthma.³⁰

In our study, adolescents were more likely to be symptomatic with SARS-CoV-2 infection as compared to younger children. Furthermore, one adolescent who was a diabetic patient died. It has been reported that teenagers infected with SARS-CoV-1, similar to adults, may develop severe illness.¹

Our study has strengths. We enrolled a relatively large number of children with asthma infected with SARS-CoV-2 from many countries, thus were able to assess factors associated with clinical manifestations and outcome of COVID-19. The limitation of our study was that there may be reporting bias in a survey. The number of cases varied substantially between countries and the number of cases from Spain accounted for more than 50% of cases. Furthermore, the severity of COVID-19 was heterogeneous between countries. Moreover, we did not specify the duration of follow-up of SARS-CoV-2 infection. Although a few patients have reported sequelae after acute SARS-CoV-2 infection, we were not able to clearly investigate long COVID.

In conclusion, asthmatic children did not have a high frequency of severe COVID-19. SARS-CoV-2 infection was associated with asthma exacerbations, but the overlap of symptoms

between COVID-19 and asthma makes it difficult to disentangle the relative contributions of COVID-19 and asthma. The use of inhaled bronchodilators was associated with a change of asthma medications, indicating that over-reliance on inhaled bronchodilator may not be appropriate. The use of ICS appears to be safe in children with asthma during the pandemic of COVID-19.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

Chen-Yuan Chiang: Conceptualization (lead); Formal analysis (lead); Methodology (equal); Writing – original draft (lead); Writing – review & editing (equal). **Philippa Ellwood:** Conceptualization (supporting); Data curation (supporting); Methodology (equal); Project administration (equal); Writing – review & editing (equal). **Eamon Ellwood:** Conceptualization (supporting); Data curation (lead); Project administration (equal); Software (lead); Writing – review & editing (equal). **Luis Garcia-Marcos:** Conceptualization (supporting); Investigation (equal); Methodology (equal); Writing – review & editing (equal). **Refiloe Masekela:** Conceptualization (supporting); Methodology (equal); Writing – review & editing (equal). **Innis Asher:** Conceptualization (supporting); Methodology (equal); Project administration (equal); Resources (lead); Writing – review & editing (equal). **Hector Badelino:** Investigation (equal); Writing – review & editing (equal). **Alberto Bercedo Sanz:** Investigation (equal); Writing – review & editing (equal). **Konstantinos Douros:** Investigation (equal); Writing – review & editing (equal). **Asma El Sony:** Conceptualization (supporting); Investigation (equal); Writing – review & editing (equal). **Carlos González Díaz:** Investigation (equal); Writing – review & editing (equal). **MS Albi Rodríguez:** Investigation (equal); Writing – review & editing (equal). **Ana Moreno-Salvador:** Investigation (equal); Writing – review & editing (equal). **Luis F Pérez-Martini:** Investigation (equal); Writing – review & editing (equal). **Nelson A Rosário:** Investigation (equal); Writing – review & editing (equal). **Andrei Shpakou:** Investigation (equal); Writing – review & editing (equal). **Shairbek Sulaimanov:** Investigation (equal); Writing – review & editing (equal). **Marzieh Tavakol:** Investigation (equal); Writing – review & editing (equal). **Jose Valverde-Molina:** Investigation (equal); Writing – review & editing (equal). **Abdullah A Yousef:** Investigation (equal); Writing – review & editing (equal). **Neil Pearce:** Conceptualization (supporting); Formal analysis (supporting); Methodology (equal); Writing – review & editing (equal).

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/pai.13709>.

DATA AVAILABILITY STATEMENT

Access to data for non GAN researchers will require a formal request to the GAN Steering Group for consideration, by submission of a written proposal and on acceptance, a signed data access agreement.

Open Research



PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/pai.13709>.

Supporting Information



Filename	Description
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Appendix

The GAN COVID Study Group

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On-line only Supporting information

eMethods

Clinical manifestations and outcome of COVID-19 among asthmatic children: Questionnaire by Global Asthma Network

eTables

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3. eTable 3. Factors associated with change of asthma medicines associated with SARS-CoV-2 infection
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Clinical manifestations and outcome of COVID-19 among asthmatic children

Questionnaire by Global Asthma Network

Please provide information on children with asthma who have a positive RT-PCR test for SARS-CoV-2. Please complete one questionnaire for each relevant child.

Date of survey completion _____
Name of Principal Investigator _____
Email of Principal Investigator _____
Name of medically trained colleague (if applicable) _____
GAN Centre Name _____
Country/Geographical location of Centre _____

1. Please specify where the child with positive SARS-CoV-2 test was identified (please mark one answer)
☐ A clinical practice of the participant
☐ A hospital or other medical facility
☐ Household contact examination
☐ School-based contact examination
☐ Others, specify: _____
2. What specimen was used for testing in this child? (please mark one answer)
☐ Nasopharyngeal swab
☐ Oral swab
☐ Both Nasopharyngeal swab and Oral swab
☐ Saliva
☐ Others, specify: _____
3. SARS-CoV-2 in this child was identified by which lab test? (please mark one answer)
☐ In-house RT-PCR
☐ Roche Cobas SARS-CoV-2
☐ Cepheid Xpert Xpress SARS-CoV-2
☐ Abbott ID NOW COVID-19
☐ Others, specify: _____
4. Was there known exposure to SARS-CoV-2? (please mark one answer)
☐ Exposure in family
☐ Exposure in school
☐ Other known exposure, specify: _____
☐ Multiple exposures, specify: _____
☐ Unknown exposure
5. National identification number of the child: _____ (not available ☐)
6. Date of birth of the child: _____ dd mm yyyy
7. Age of the child when the child had the positive test for SARS-CoV-2
Year: _____ Months: _____
8. Date of positive test for SARS-CoV-2: _____ dd mm yyyy
9. Sex of the child: ☐ boy ☐ girl ☐ unknown
10. Please indicate the frequency of each inhaler that the child used for asthma control in past 3 months before the positive test for SARS-CoV-2?

	Not used	As needed	Everyday
Short acting β - agonists (SABA)			
Long acting β - agonists (LABA)			
Inhaled corticosteroid (ICS)			
<i>Combination ICS and LABA</i>			

11. Was the child treated with any tablets, capsules, pills, or liquids for asthma in past 3 months before the positive test for SARS-CoV-2?

☐ No ☐ Yes (please indicate name of the medicines and frequency of use)

	As needed	Everyday
Leukotriene receptor antagonist		
<i>(name of the medicine)</i>		
<i>(name of the medicine)</i>		
<i>(name of the medicine)</i>		

12. Other comorbidities

☐ No ☐ Yes (if yes, please indicate)

Immune suppression

☐ No

☐ Yes

Obesity

☐ No

☐ Yes

Diabetes

☐ No

☐ Yes

Malignancy

☐ No

☐ Yes

Seizure

☐ No

☐ Yes

Sickle cell disease

☐ No

☐ Yes

Bronchopulmonary dysplasia

☐ No

☐ Yes

Cystic fibrosis

☐ No

☐ Yes

Other chronic respiratory

conditions, excluding asthma

☐ No

☐ Yes

specify: _____

Congenital heart disease

☐ No

☐ Yes

Other congenital disease

☐ No

☐ Yes,

specify: _____

13. Was the child symptomatic after the positive test for SARS-CoV-2?

☐ Asymptomatic

☐ Symptomatic (please indicate symptoms in Table)

	Yes	No	Unknown
Abdominal pain			
Apnoea			
Chest pain			
Conjunctivitis			
Cough			
Cyanosis			
Dehydration			
Diarrhoea			
Fatigue			
Fever			
Headache			
Myalgia			
Nausea or vomiting			
Rash			

Rhinorrhoea			
Seizure			
Shortness of breath			
Smell reduction			
Sore throat			
Tachypnoea*			
Tachycardia†			
Taste reduction			
Wheeze			
Other Specify _____			

*Tachypnoea refers to a respiratory rate higher than the upper limit of the normal range, according to age. The normal ranges of respiratory rate (in breaths per minute) were as follows: 40 to 60 for newborns, 30 to 40 for children from 1 month to less than 1 year of age, 25 to 30 for those 1 to 3 years of age, 20 to 25 for those 4 to 7 years of age, 18 to 20 for those 8 to 14 years of age, and 12 to 20 for those older than 14 years of age. (N Engl J Med 2020;383;2:187-190)

†Tachycardia refers to a pulse rate higher than the upper limit of the normal range, according to age. The normal ranges of pulse rate (in beats per minute) were as follows: 120 to 140 for newborns, 110 to 130 for children from 1 month to less than 1 year of age, 100 to 120 for those 1 to 3 years of age, 80 to 100 for those 4 to 7 years of age, 70 to 90 for those 8 to 14 years of age, and 60 to 70 for those older than 14 years of age. (N Engl J Med 2020;383;2:187-190)

14. Body temperature at presentation:

☐ ≤37.5 ☐ 37.6-38.0 ☐ 38.1-39.0 ☐ >39.0

15. Was there exacerbation of asthma associated with the positive test for SARS-CoV-2 (within 10 days)?

☐ No ☐ Yes

16. Was there any change of treatment of asthma associated with the positive test for SARS-CoV-2?

☐ No ☐ Yes (If yes, please indicate what change has been done)

	Newly prescribed	Increase dosage	Increase frequency
Short acting β - agonists (SABA)			
Long acting β - agonists (LABA)			
Inhaled corticosteroid (ICS)			
<i>Combination ICS and LABA</i>			
Leukotriene receptor antagonist			
<i>(name of other medicine)</i>			

17. Did the child have a chest radiograph?

☐ No ☐ Yes

18. If yes, was there pneumonia?

☐ No ☐ Yes

19. Did the child have a chest CT scan?

☐ No ☐ Yes

20. If yes, was there any opacities on chest CT?

☐ No ☐ Yes

21. Please indicate the severity of COVID-19 of the child (Lancet Infect Dis 2020; 20(6): 689-96)

☐ Mild disease: upper respiratory symptoms (eg, pharyngeal congestion, sore throat, and fever) for a short duration or asymptomatic infection. No abnormal radiographic and septic presentation

- ☐ Moderate disease: Mild pneumonia; Symptoms such as fever, cough, fatigue, headache, and myalgia; No complications and manifestations related to severe conditions
- ☐ Severe disease: Mild or moderate clinical features, plus any manifestations that suggest disease progression, including rapid breath (≥ 70 breaths per min for infants aged <1 year; ≥ 50 breaths per min for children aged >1 year), or Hypoxia, or Lack of consciousness, depression, coma, convulsions, or dehydration, difficulty feeding, gastrointestinal dysfunction, or Myocardial injury, or Elevated liver enzymes, or Coagulation dysfunction, rhabdomyolysis, and any other manifestations suggesting injuries to vital organs
- ☐ Critical illness: rapid disease progression, plus any other conditions, such as Respiratory failure with need for mechanical ventilation (eg, ARDS, persistent hypoxia that cannot be alleviated by inhalation through nasal catheters or masks), or Septic shock, or organ failure that needs monitoring in the intensive care unit

22. Treatment of COVID-19

- | | | |
|------------------------|-----------------------------|------------------------------|
| Hydroxychloroquine | ☐ No | ☐ Yes |
| Immune globulin | ☐ No | ☐ Yes |
| Interferon alfa | ☐ No | ☐ Yes |
| Lopinavir–ritonavir | ☐ No | ☐ Yes |
| Macrolides | ☐ No | ☐ Yes |
| Oseltamivir | ☐ No | ☐ Yes |
| Oxygen inhalation | ☐ No | ☐ Yes |
| Remdisivir | ☐ No | ☐ Yes |
| Steroids, oral | ☐ No | ☐ Yes |
| Steroids, systemic | ☐ No | ☐ Yes |
| CPAP/BiPAP* | ☐ No | ☐ Yes |
| Intubation ventilation | ☐ No | ☐ Yes |
| ECMO* | ☐ No | ☐ Yes |
| Others, | ☐ No | ☐ Yes |

specify: _____

* BiPAP, bilevel positive airways pressure; CPAP, continuous positive airways pressure; ECMO, Extracorporeal membrane oxygenation

23. Was the child admitted to hospital

- ☐ No ☐ Yes

24. If yes, what was the number of days of hospitalization: _____ days

25. Did the child have multisystem inflammatory syndrome (JAMA 2020; **324**(3): 259-69)?

- ☐ No ☐ Yes

26. Outcome of COVID-19

- ☐ Recovered, no sequelae
- ☐ Recovered, with sequelae
Specify sequelae: _____
- ☐ Died

eTable 1. Comorbidity and symptoms of COVID-19 in 169 asthmatic children infected with SARS-CoV-2

	Number	Percentage
Comorbidities other than asthma	29	17.2
Immune suppression	1	0.6
Obesity	12	7.1
Diabetes	1	0.6
Malignancy	0	0
Seizure	3	1.8
Sickle cell disease	0	0
Bronchopulmonary dysplasia	8	4.7
Cystic fibrosis	0	0
Other chronic respiratory conditions*	8	4.7
Congenital heart disease	1	0.6
Other congenital disease†	5	3
Body temperature		
≤37.5	94	55.0
37.6-38.0	34	20.1
38.1-39.0	42	24.9
Symptomatic	111	65.7
Abdominal pain	17	10.0
Apnea	3	1.8
Chest pain	16	9.5
Conjunctivitis	11	6.5
Cough	74	43.8
Cyanosis	8	4.7
Dehydration	6	3.6
Diarrhoea	21	12.4
Fatigue	58	34.3
Headache	71	42.0
Myalgia	35	20.7
Nausea or vomiting	21	12.4
Rash	4	2.4
Rhinorrhoea	59	34.9
Seizure	0	0
Shortness of breath	23	13.6
Smell reduction	43	25.4
Sore throat	38	22.5
Tachypnoea	15	8.9
Tachycardia	10	5.9
Taste reduction	36	21.3
Wheeze	26	15.4
Others*	10	5.9

*Allergic rhinitis, 5; sinusitis, 3; protracted bacterial bronchitis, 1.

† Chronic neuropathy (cerebral palsy), 3; short stature, 1, benign hyperphenylalaninemia, 1.

eTable 2. Factors associated with being symptomatic associated with SARS-CoV-2 infection

	Total N=	Symptomatic N (%)	Univariable** OR(95% CI)	Multivariable‡ adjOR(95% CI)
Total	169	111 (65.7)		
Age at infection (years)				
<10	85	47 (55.3)	reference	reference
10 – 13.9	60	42(70.0)	1.95 (0.89-4.25)	1.78(0.80-3.95)
≥ 14	24	22(91.7)	9.71 (2.00-47.13)	10.67(2.14-52.95)
Sex				
Female	59	37(62.7)	reference	reference
Male	110	74(67.3)	1.41(0.65-3.06)	1.45(0.65-3.24)
High income countries				
No	60	56(93.3)	reference	reference
Yes	109	55(50.5)	0.07(0.02-0.21)	0.08(0.03-0.26)
Exposure to COVID-19 cases				
Unknown	22	19(86.4)	reference	reference
Family	121	79(65.3)	0.34(0.08-1.37)	0.34(0.08-1.39)
Other exposure	26	13(50.0)	0.22(0.04-1.12)	0.22(0.04-1.12)
Comorbidity				
No	140	87(62.1)	reference	reference
Yes	29	24(82.8)	1.36(0.41-4.60)	1.36(0.39-4.68)
Use of bronchodilator*†				
No	102	55(53.9)	reference	reference
Yes	67	56(83.6)	1.42(0.56-3.60)	1.40(0.54-3.62)
Use of inhaled corticosteroid†				
No	110	78(70.9)	reference	reference
Yes	59	33(55.9)	0.80(0.37-1.74)	0.80(0.36-1.76)
Use of combined inhaler†				
No	132	81(61.4)	reference	reference
Yes	37	30(81.1)	2.98(1.09-8.19)	2.79(0.99-7.81)
Use of Leukotriene receptor antagonist†				
No	149	97(65.1)	reference	reference
Yes	20	14(70)	1.16(0.35-3.86)	0.89(0.25-3.17)

*Short acting beta agonist or Long acting beta agonist

† daily or as needed

** adjusted for age, sex, and countries

‡ adjusted for age, sex, countries, exposure to COVID-19 cases, and comorbidity

eTable 3. Factors associated with change of asthma medicines associated with SARS-CoV-2 infection

	Total N=	Treatment change N (%)	Univariable** OR(95% CI)	Multivariable‡ adjOR(95% CI)
Total	169	53 (31.4)		
Age at infection (years)				
<5	17	6(35.3)	reference	reference
5 - 9.9	68	16(23.5)	0.66(0.19-2.28)	0.77(0.20-2.93)
10 – 13.9	60	20(33.3)	1.00(0.29-3.44)	1.01(0.27-3.79)
≥ 14	24	11(45.8)	1.55(0.38-6.27)	1.83(0.40-8.33)
Sex				
Female	59	20(33.9)	reference	reference
Male	110	33(30.0)	0.81(0.38-1.71)	0.80(0.36-1.78)
High income countries				
No	60	34(56.7)	reference	reference
Yes	109	19(17.4)	0.17(0.08-0.34)	0.27(0.12-0.60)
Exposure to COVID-19 cases				
Unknown	22	11(50.0)	reference	reference
Family	121	39(32.2)	0.60(0.21-1.67)	0.62(0.22-1.76)
Other exposure	26	3(11.5)	0.18(0.04-0.92)	0.16(0.03-0.87)
Comorbidity				
No	140	38(27.1)	reference	reference
Yes	29	15(51.7)	1.69(0.65-4.37)	1.64(0.60-4.47)
Severity of COVID-19				
Asymptomatic/mild	151	40(26.5)	reference	reference
Moderate/severe	18	13(72.2)	2.61(0.78-8.69)	2.64(0.77-9.13)
Use of bronchodilator*†				
No	102	18(17.7)	reference	reference
Yes	67	35(52.2)	2.68(1.18-6.07)	2.39(1.02-5.63)
Use of inhaled corticosteroid†				
No	110	34(30.9)	reference	reference
Yes	59	19(32.2)	2.04(0.89-4.65)	1.92(0.82-4.52)
Use of combined inhaler†				
No	132	40(30.3)	reference	reference
Yes	37	13(35.1)	1.02(0.42-2.51)	0.93(0.36-2.42)
Use of Leukotriene receptor antagonist†				
No	149	44(29.5)	reference	reference
Yes	20	9(45.0)	1.70(0.58-5.00)	1.74(0.56-5.41)

*Short acting beta agonist or Long acting beta agonist

† daily or as needed

**adjusted for age, sex, and countries

‡ adjusted for age, sex, countries, exposure to COVID-19 cases, comorbidity and severity of COVID-19.

eTable 4. Factors associated with hospitalization with SARS-CoV-2 infection

	Total N=	Hospitalization N (%)	Univariable** OR(95% CI)	Multivariable‡ adjOR(95% CI)
Total	169	21 (12.4)		
Age at infection (years)				
<5	17	4(23.5)	reference	reference
5 - 9.9	68	4(5.9)	0.19(0.03-1.15)	0.25(0.02-2.76)
10 – 13.9	60	10(16.7)	0.63(0.13-3.21)	0.62(0.07-5.41)
≥ 14	24	3(12.5)	0.31(0.05-2.11)	0.08(0.01-1.37)
Sex				
Female	59	8(13.6)	reference	reference
Male	110	13(11.8)	0.77(0.25-2.37)	0.42(0.09-2.03)
High income countries				
No	60	20(33.3)	reference	reference
Yes	109	1(0.92)	0.02(<0.01-0.14)	0.03(<0.01-0.31)
Exposure to COVID-19 cases				
Unknown	22	5(22.7)	reference	reference
Family	121	13(10.7)	0.77(0.19-3.11)	0.81(0.14-4.57)
Other exposure	26	3(11.5)	3.60(0.36-36.22)	4.61(0.27-78.77)
Comorbidity				
No	140	11(7.9)	reference	reference
Yes	29	10(34.5)	3.20(0.94-10.92)	2.80(0.61-12.95)
Severity of COVID-19				
Asymptomatic/mild	151	8(5.3)	reference	reference
Moderate/severe	18	13(72.2)	22.61(4.71-108.57)	24.62(4.63-130.90)
Use of bronchodilator*†				
No	102	3(2.9)	reference	reference
Yes	67	18(26.9)	2.95(0.71-12.25)	1.98(0.34-11.43)
Use of inhaled corticosteroid†				
No	110	15(13.6)	reference	reference
Yes	59	6(10.2)	2.13(0.55-8.16)	2.88(0.47-17.73)
Use of combined inhaler†				
No	132	16(12.1)	reference	reference
Yes	37	5(13.5)	0.71(0.19-2.62)	0.49(0.08-2.87)
Use of Leukotriene receptor antagonist†				
No	149	17(11.4)	reference	reference
Yes	20	4(20.0)	1.41(0.32-6.15)	1.75(0.30-10.27)

*Short acting beta agonist or Long acting beta agonist

† daily or as needed

**adjusted for age, sex, countries

‡ adjusted for age, sex, countries, exposure to COVID-19 cases, comorbidity and severity of COVID-19.